

REMARKS

Claims 1-78 are cancelled and new claims 79-107 are added by this amendment. The new claims are presented to clarify and organize the claimed subject matter. A chart showing the support for the new claims in previously pending claims or the specification as filed is provided as Appendix A. All the limitations of claims 79 and 82-107 were present in the previously pending claims. The new limitations added in claims 80 and 81 are supported in the specification at page 4, lines 2-5 and 11-14. No new matter is added with the presentation of the new claims.

All the previously pending claims had been allowed, but currently stand rejected under 35 U.S.C. § 102 and 103 as allegedly anticipated by U.S. Patent No. 5,510,121 ("Rhee") or allegedly obvious over Rhee in view of WO 97/3259 ("Radomsky 1"), U.S. Patent No. 5,658,882 ("Celeste"), Vercruysse et al., Campoccia et al., U.S. Patent No. 5,336,767 (della Valle), and/or U.S. Patent No. 5,942,499 ("Radomsky 2"). These references were cited by Applicants in an Information Disclosure Statement after their submission by an Opponent in the opposition of the corresponding European case. Because Applicants had previously provided the Examiner with the Opponent's submissions, Applicants now submit a copy of the European Patent Office's preliminary opinion on patentability, stating that the claims appear to be both novel and inventive over the cited references. Applicants also include a copy of the claims currently pending in Europe. Applicants understand that the Examiner need not consider the EPO's opinion, but request such consideration because the European Patent Office's opinion is consistent with the arguments presented below.

The Examiner has already concluded that the claimed invention is patentable over what Applicants believe is the closest prior art, U.S. Patent No. 5,939,323 ("Valentini"). Applicants respectfully submit that the newly cited references are significantly less relevant to the patentability of the currently pending claims. The multiple insufficiencies of these references are set forth below.

REJECTION UNDER 35 U.S.C. § 102(b)

The Examiner has rejected claim 1 as allegedly lacking novelty under 35 U.S.C. § 102(b) over Rhee. The Examiner contends that Rhee discloses the use of hyaluronic acid esters and PEG in corresponding compositions, and that these compositions can contain TCP and osteogenic factors, as is currently claimed. Applicants traverse.

Applicants have presented three different independent claims that correspond essentially to original claim 1 (new claims 79-81). Claim 79 reads as follows:

A composition for injectable delivery of osteogenic proteins to a patient comprising

- (a) an osteogenic protein;
- (b) an injectable hyaluronic acid ester; and
- (c) a pore former selected from a liquid pore former or sodium bicarbonate,

wherein the composition is injectable through the skin of a patient.

This claim encompasses an injectable composition comprising three distinct components: an osteogenic protein, a hyaluronic acid ester, and a pore former selected from a liquid pore former or sodium bicarbonate. Rhee does not disclose such a composition. Instead, Rhee describes a composition with two components: a

hyaluronic acid-PEG conjugate and a growth factor. Unlike the instantly claimed composition, which contains molecules of hyaluronic acid esters and separate molecules of pore formers (such as PEG) as discrete entities within the composition, Rhee only describes a composition containing molecules of hyaluronic acid-PEG conjugate. In this conjugated form, PEG itself does not exist and thus the Rhee composition does not contain a pore former as required by Applicants claims. Accordingly, Rhee does not teach the three-element composition of claim 79.

Claims 80 and 81 read as follows:

80. A composition for injectable delivery of osteogenic proteins to a patient comprising

- (a) an osteogenic protein;
- (b) an injectable hyaluronic acid ester; and
- (c) a pore former selected from a liquid pore former or sodium bicarbonate,

wherein the composition is injectable through the skin of a patient, and upon injection the osteogenic protein and hyaluronic acid ester form a porous precipitate.

81. A composition for injectable delivery of osteogenic proteins to a patient comprising

- (a) an osteogenic protein;
- (b) an injectable hyaluronic acid ester; and
- (c) a pore former selected from a liquid pore former or sodium bicarbonate,

wherein the composition is injectable through the skin of a patient, and upon injection the pore former is extracted from the osteogenic protein and hyaluronic acid ester by solubilization in situ.

These claims requires that, when outside the body, the composition contains a pore former, and that, upon injection, the composition becomes a porous scaffold when the pore former is extracted out of the composition by solubilization and the composition precipitates. These features are not taught or suggested by Rhee. Rhee only teaches conjugates of hyaluronic acid and PEG. Because the PEG is covalently bound to the hyaluronic acid, it will not be extracted out of the composition after injection and thus, pores will not be formed.

Furthermore, Rhee does not enable one of skill in the art to make a composition comprising a hyaluronic acid ester and an osteogenic protein. Rhee specifically teaches that a hyaluronic acid ester should not be used when administering osteogenic compositions because the ester bond will hydrolyze too quickly to allow bone repair, stating “[w]hen making bone repair compositions intended to persist for long periods of time *in vivo*, the linkage between the glycosaminoglycan and synthetic polymer may be an ether linkage in order to avoid deterioration due to the hydrolysis of the ester linkages” (col. 27, lines 43-47, emphasis added). Rhee thus teaches that a hyaluronic acid ester should not be used to deliver an osteogenic protein. Therefore, Applicants’ claims, which specifically recite a combination of hyaluronic acid esters and osteogenic proteins, are not anticipated or rendered obvious by the teachings of Rhee.

Accordingly, Rhee does not teach all the limitations of claims 79, 80, or 81 and does not anticipate the claims under 35 U.S.C. § 102(b).

REJECTION UNDER 35 U.S.C. § 103

The Examiner rejected claims 1, 14-16, and 22-78 as allegedly obvious over Rhee in view of WO 97/32591 (“Radomsky 1”), and/or U.S. Patent No. 5,658,882

("Celeste") in view of Vercruysse & Prestwich, *Critical Reviews in Therapeutic Drug Carrier Systems* 515(5):519-55 (1988), and/or Campoccia et al., *Biomaterials* 19:2101-27 (1998) in view of U.S. Patent No. 5,336,767 ("della Valle") or U.S. Patent No. 5,942,499 (Radomsky 2").

I. The Claimed Subject Matter

A. Independent Claims 79-81

Claim 79, the broadest independent claim, recites the following limitations (emphasis added):

A composition for injectable delivery of osteogenic proteins to a patient comprising

- (a) an osteogenic protein;
- (b) an injectable hyaluronic acid ester; and
- (c) a pore former selected from a liquid pore former or sodium bicarbonate,

wherein the composition is injectable through the skin of a patient.

This claim has four key limitations. Three are distinct structural components of the composition and the fourth is a physical property. The three structural components are (1) an osteogenic protein, (2) a hyaluronic acid ester, and (3) a pore former selected from a liquid pore former or sodium bicarbonate. The physical property required by claim 79 is that the composition be injectable through the skin of a patient. Claims 80 and 81 have the further limitation that the composition must form a porous scaffold in vivo, another physical property. For the reasons set forth in detail below, none of the cited references, alone or in combination, teach or suggest a composition containing all of these limitations.

B. Independent Claims 103 and 107

Claims 103 and 107 recite a specific hyaluronic acid ester, Hyaff11p65. As demonstrated in detail below, none of the art cited by the Examiner discloses, teaches, or suggests compositions comprising Hyaff11p65, nor do they teach or suggest the advantages of this ester over other known Hyaff11 benzyl esters.

II. The Prior Art

A. Rhee

The Examiner contends that Rhee teaches conjugates of hyaluronic acid and PEG via ester bonds, thereby disclosing “the use of hyaluronic acid esters and PEG” in pharmaceutical compositions, and that these compositions can contain bone morphogenetic proteins, and that the conjugates can be used as injectable delivery systems.

However, as explained above in connection with the rejection under 35 U.S.C. § 102, Rhee does not teach a composition comprising the three distinct components (osteogenic protein, hyaluronic acid ester, and pore former). Instead, Rhee teaches that the hyaluronic acid must be conjugated to PEG through a variety of linkages, including, in one embodiment, an ester linkage. This single hyaluronic acid-PEG conjugate is in no way equivalent to a true hyaluronic acid ester and a pore former for at least two reasons. First, in this conjugated form, PEG does not and cannot function as a pore former. Second, the “ester linkage” of Rhee’s conjugate to PEG does not impart the same properties (e.g., solubility, viscosity) on the hyaluronic acid as those possessed by the hyaluronic acid ester of the amended claims.

Claims 80 and 81 additionally require the presence of pores in the composition after injection. Rhee does not teach or suggest to one of skill in the art how to make a porous composition. In fact, Rhee teaches away from such a composition by requiring that the PEG (a potential pore former) be covalently linked to the hyaluronic acid, ensuring that it will not be extracted out of the composition to form pores.

Rhee also teaches, as noted above, that if the composition is to be used to induce bone growth, it should not contain an ester bond, thereby teaching away from the claimed invention. Thus, even if Rhee could be construed to recite a hyaluronic acid ester similar to those currently claimed (Hyaaff benzyl esters), it specifically teaches away from using an ester when making bone repair compositions. Accordingly, Rhee teaches a composition that does not have a distinct pore former component, cannot form pores, and shouldn't be used for delivery of osteogenic proteins, all of which are required by the pending claims. None of the remaining cited references address these deficiencies.

B. Radomsky 1

The Examiner contends that Radomsky 1 discloses "a bone growth-promoting composition comprising hyaluronic acid and a growth factor," and that this solution "should have a viscosity which allows for injection of the composition through a syringe or catheter." The Examiner further states that Radomsky 1 discloses the desirability of a residence time of 3-30 days. However, Radomsky 1 does not teach or suggest a composition comprising a hyaluronic acid ester, a pore former, or pores. Accordingly, Radomsky fails to teach all the limitations of the claims. Radomsky 1 further fails to suggest modification of Rhee to achieve the claimed invention.

C. Celeste

The Examiner contends that Celeste discloses compositions containing BMP-12, BMP-13, and MP52 and a hyaluronic acid derivative as a sequestering device. Celeste does not teach or suggest a composition comprising a hyaluronic acid ester, pores, or a pore former, let alone the specifically claimed pore formers. Accordingly, Celeste neither teaches all the limitations of the claims, nor addresses any of the deficiencies of Rhee and Radomsky 1.

D. Vercruysse

The Examiner contends that Vercruysse discloses hyaluronic acid esters, specifically Hyaff11 benzyl esters, and further discloses the use of microspheres of these esters for delivery of growth factors. However, Vercruysse does not disclose or suggest injectable versions of these esters, nor does it teach or suggest that the compositions contain pores or pore formers, let alone the specifically claimed pore formers. Vercruysse does not disclose Hyaff11p65. Vercruysse also fails to suggest alteration of the teachings of Rhee alone or in combination with other cited references to achieve the claimed invention.

E. Campoccia

The Examiner contends that Campoccia discloses esterified forms of hyaluronic acid, such as Hyaff11, and their properties. In particular, the Examiner states that Campoccia teaches that the esterification of hyaluronic acid has a profound effect on its interaction with water—the higher the esterification percentage, the lower the solubility in water. Campoccia also describes the degradation profiles of Hyaff11 and Hyaff11p75, and concludes that partial esters degrade more quickly than total esters

because partial esters are more flexible and hydrated than total esters. However, Campoccia disclose that any of these hyaluronic acid esters are injectable, that they could be injected after the addition of pore formers, nor does Campoccia disclose compositions containing pore formers, let alone the specifically claimed pore formers, or that they should contain pores in situ. Campoccia also fails to disclose Hyaff11p65. More importantly, Campoccia provides no reason to disregard the explicit teaching away for the use of hyaluronic acid esters and osteogenic proteins set forth in Rhee.

F. della Valle

The Examiner contends that della Valle discloses partial and complete hyaluronic acid esters, such as Hyaffs. The Examiner further contends that della Valle states that these esters have the same physical-chemical, pharmacological, and therapeutic properties as hyaluronic acid, but are more stable. However, in direct contradiction to that statement, the Examiner admits that della Valle discloses that the solubility properties of these esters differ significantly from those of non-esterified hyaluronic acid. Thus, one cannot draw the conclusion from della Valle that hyaluronic acid esters and hyaluronic acid have the same physical-chemical properties.

The Examiner also contends that della Valle states that the esters may be used for intraarticular injections and may be used in conjunction with growth factors. However, as Applicants have discussed at length in previous responses, rendering a hyaluronic acid ester composition injectable is a complicated process involving significant inventive thought and effort. Accordingly, simply mentioning that a composition may be used for injection does not provide one of skill in the art with a reasonable expectation of success in actually making this composition injectable. And

finally, as with all the cited references, della Valle does not disclose that the compositions could be injected after the addition of pore formers, that these compositions should contain pore formers, let alone the specifically claimed pore formers, or that it should contain pores in situ. della Valle also fails to teach Hyaff11p65. Finally, della Valle does not suggest any reason to doubt Rhee's teaching away from the use of hyaluronic acid esters and osteogenic proteins.

G. Radomsky 2

The Examiner cited a second Radomsky reference, a continuation-in-part of the reference discussed above, and contends that this patent discloses a composition comprising a hyaluronic acid, a growth factor, and sucrose or sodium citrate. The Examiner contends that, according to Applicants' specification, sucrose and sodium citrate are pore formers. Radomsky 2 teaches the addition of sucrose and sodium citrate to its compositions to maintain bioactivity and pH levels. However, Applicants' specification provides the first identification of these compositions as pore formers for injectable hyaluronic acid ester compositions. Thus, it would require impermissible hindsight for one of skill in the art would recognize their use for this particular purpose from the prior art. Furthermore, the pending claims specifically exclude any pore former that is not a liquid pore former or sodium bicarbonate, and Radomsky 2 does not suggest the inclusion of these pore formers. Finally, Radomsky 2 does not mention esterification or ester bonds, supporting Rhee's teaching away from using such modifications when delivering osteogenic proteins.

IV. Conclusion

A. Claims 79-102

The invention of claims 79-102 requires that either a liquid pore former or sodium bicarbonate be present in the composition. Furthermore, the claims require that the composition be injectable through the skin of the patient, and claims 80 and 81 specifically require that the composition form a porous scaffold in situ. Not a single reference cited by the Examiner discusses the use of pore formers in the disclosed hyaluronic acid compositions. Not a single reference discusses the presence of a porous scaffold in situ. And not a single reference teaches how to render a composition containing a hyaluronic acid ester, an osteogenic protein, and a pore former injectable. And nothing in any reference suggests that Rhee is wrong in suggesting that the combination of ester bonds and osteogenic proteins is not desirable. Accordingly, the references as a whole do not teach these limitations either.

In the six references cited by the Examiner, only one (della Valle) mentions the possibility of using an injectable formulation of hyaluronic acid esters. No references discuss the possibility of using an injectable composition containing pore formers. The single sentence regarding intraarticular injection in della Valle is not sufficient for one of skill in the art to have a reasonable expectation of success in actually preparing and using an injectable composition, particularly an injectable composition containing pore formers.

As discussed in detail when differentiating the claims over Valentini, rendering each partial and complete ester of hyaluronic acid injectable requires a careful selection of solvent (either aqueous or organic, depending on the level of esterification) and pore

former. With highly esterified hyaluronic acids, the solvent must be organic and pore formers must be present to form the desired scaffolds *in vivo*. With lower levels of esterification, the pore formers are less necessary and aqueous buffers may be used. Then, the composition must be formulated so as to be injectable through a needle, but still viscous enough to form a scaffold upon deposit in a bone or tissue defect. This process is complicated by the addition of pore formers, which are generally difficult to inject. This information regarding the requirements for injectable formulations is necessary to practice the claimed invention and is provided for the first time in Applicants' specification, not in the cited art. Accordingly, even the combination of all six references fails to teach or suggest the requirement that the compositions contain specific pore formers and further fails to provide the requisite expectation of success in rendering a hyaluronic acid ester injectable through the skin of a patient. In light of these deficiencies, Applicants request that the rejection of the claims under 35 U.S.C. § 103 be withdrawn.

B. Claims 103-107

Claims 103-107 require the presence of a specific Hyaff formulation, Hyaff11p65. This ester was previously found to be clear of the art (3/21/05 O.A., p. 2). In that Office Action, the Examiner stated that

[t]his ester does not appear to have been known in the art prior to the instant disclosure, see Campoccia, et al. (1998) and Radice et al. (US 6,669,471 [sic]), and was not disclosed in a publication until WO 03/099992 (all previously cited). Given that the instant disclosure provides evidence of the advantage of this ester over other known Hyaff11 esters disclosed in Valentini, a rejection as obvious would not be sustainable and was not made. While della Valle, et al. (US 4,581,521) discloses methods of preparing various full and partial hyaluronic acid ester including benzyls used in

Hyaff11, they do not explicitly disclose or reasonably suggest this particular ester or its advantages as instantly disclosed. (3/21/05 O.A., p. 2.)

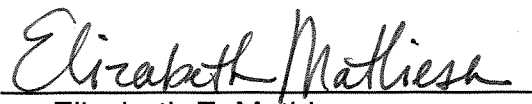
However, in this Office Action, the Examiner states that "it would have been obvious to one of ordinary skill in the art to combine either Vercruysse and/or Campoccia to use hyaluronic acid esters from 0% to 100%" (5/9/06 O.A., p. 7). This appears to be the only rationale for the rejection of previously allowed claims 14 and 16 (now claims 103 and 107). However, neither Vercruysse or Campoccia recognized the advantage of Hyaff11p65 over known Hyaff11 formulations, i.e., its increased solubility in aqueous buffer while surprisingly providing a structure in situ that allows for cell ingrowth. Accordingly, as previously recognized by the Examiner, the claims reciting Hyaff11p65 are not obvious over the cited art. Accordingly, Applicants request reconsideration and withdrawal of the rejection of the claims specifically reciting this ester.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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Appendix A--Chart Showing Support for New Claims

New Claim	Original Claim/Support in Specification
<p>79. A composition for injectable delivery of osteogenic proteins to a patient comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; (b) an injectable hyaluronic acid ester; and (c) a pore former selected from a liquid pore former or sodium bicarbonate, <p>wherein the composition is injectable through the skin of a patient.</p>	<p>1. A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; and (b) an injectable hyaluronic acid ester, <p>wherein said admixture is injectable through the skin of a patient and wherein said admixture</p> <ul style="list-style-type: none"> (i) comprises a pore former selected from a liquid pore former or sodium bicarbonate or (ii) does not include a pore former.
<p>80. A composition for injectable delivery of osteogenic proteins to a patient comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; (b) an injectable hyaluronic acid ester; and (c) a pore former selected from a liquid pore former or sodium bicarbonate, <p>wherein the composition is injectable through the skin of a patient, and upon injection the osteogenic protein and hyaluronic acid ester form a porous precipitate.</p>	<p>page 4, lines 2-5, 11-14.</p>
<p>81. A composition for injectable delivery of osteogenic proteins to a patient comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; (b) an injectable hyaluronic acid ester; and (c) a pore former selected from a liquid pore former or sodium bicarbonate, <p>wherein the composition is injectable through the skin of a patient, and upon injection the pore former is extracted from the osteogenic protein and hyaluronic acid ester by solubilization in situ.</p>	<p>page 4, lines 2-5, 11-14.</p>
<p>82. The composition of any one of claims 79 to 81, wherein the hyaluronic acid ester is at least 50% esterified.</p>	<p>22. The composition of claim 1, wherein the hyaluronic acid ester is at least 50% esterified.</p>
<p>83. The composition of any one of claims</p>	<p>23. The composition of claim 1, wherein</p>

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New Claim	Original Claim/Support in Specification
79 to 81, wherein the hyaluronic acid ester is at least 60% esterified.	the hyaluronic acid ester is at least 60% esterified.
84. The composition of any one of claims 79 to 81, wherein the hyaluronic acid is at least 65% esterified.	24. The composition of claim 1, wherein the hyaluronic acid is at least 65% esterified.
85. The composition of any one of claims 79 to 81, wherein the hyaluronic acid is at least 75% esterified.	25. The composition of claim 1, wherein the hyaluronic acid is at least 75% esterified.
86. The composition of any one of claims 79 to 81, wherein the hyaluronic acid is at least 80% esterified.	26. The composition of claim 1, wherein the hyaluronic acid is at least 80% esterified.
87. The composition of any one of claims 79 to 81, wherein the hyaluronic acid is 100% esterified.	27. The composition of claim 1, wherein the hyaluronic acid is 100% esterified.
88. The composition of any one of claims 79 to 81, wherein the liquid pore former is polyethylene glycol.	38. The composition of claim 1, wherein the liquid pore former is polyethylene glycol.
89. The composition of any one of claims 79 to 81, wherein the hyaluronic acid ester is solubilized in an organic solvent.	39. The composition of claim 1, wherein the hyaluronic acid ester is solubilized in an organic solvent.
90. The composition of any one of claims 79 to 81, wherein the hyaluronic acid ester is solubilized in an aqueous buffer.	40. The composition of claim 1, wherein the hyaluronic acid ester is solubilized in an aqueous buffer.
91. The composition of any one of claims 79 to 81, further comprising TCP.	41. The composition of claim 1, further comprising TCP.
92. The composition of any one of claims 79 to 81, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, and BMP-12.	42. The composition of claim 1, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, and BMP-12.
93. The composition of any one of claims 79 to 81, wherein the hyaluronic acid ester is Hyaff11.	44. A composition for delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising (a) an osteogenic protein; and (b) an injectable hyaluronic acid ester, wherein the hyaluronic acid ester is Hyaff11, wherein the admixture is injectable through the skin of the patient, and wherein said admixture (i) comprises a pore

Appendix A--Chart Showing Support for New Claims

New Claim	Original Claim/Support in Specification
	<p style="text-align: right;">former selected from a liquid pore former or sodium bicarbonate or</p> <p>(ii) does not include a pore former.</p>
<p>94. The composition of claim 93, wherein the liquid pore former is polyethylene glycol.</p>	<p>72. (Previously presented) A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; (b) Hyaff11; and (c) polyethylene glycol, <p>wherein the admixture is injectable through the skin of a patient.</p>
<p>95. The composition of claim 93, wherein the hyaluronic acid ester is solubilized in an organic solvent.</p>	<p>70. (Previously presented) A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; and (b) Hyaff11, <p>wherein the admixture is injectable through the skin of a patient and the Hyaff11 is solubilized in organic solvent.</p>
<p>96. The composition of claim 93, further comprising TCP.</p>	<p>73. (Previously presented) A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <ul style="list-style-type: none"> (a) an osteogenic protein; (b) Hyaff11; and (c) TCP, <p>wherein the admixture is injectable through the skin of a patient.</p>
<p>97. The composition of claim 93, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, and BMP-12.</p>	<p>47. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-2.</p> <p>48. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-4.</p> <p>49. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-5.</p> <p>50. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-6.</p> <p>51. (Previously presented) The composition of claim 44, wherein the</p>

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New Claim	Original Claim/Support in Specification
	<p>osteogenic protein is BMP-7. 52. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-8. 53. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-9. 54. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-10. 55. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-11. 56. (Previously presented) The composition of claim 44, wherein the osteogenic protein is BMP-12.</p>
98. The composition of any one of claims 79 to 81, wherein the hyaluronic acid ester is Hyaff11p80.	57. A composition for delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising (a) an osteogenic protein; and (b) an injectable hyaluronic acid ester, wherein the hyaluronic acid ester is Hyaff11p80, wherein the admixture is injectable through the skin of the patient and wherein said admixture (i) comprises a pore former selected from a liquid pore former or sodium bicarbonate or (ii) does not include a pore former.
99. The composition of claim 98, wherein the liquid pore former is polyethylene glycol.	58. The composition of claim 57, wherein the liquid pore former is polyethylene glycol.
100. The composition of claim 98, wherein the hyaluronic acid ester is solubilized in an organic solvent.	76. A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising (a) an osteogenic protein; and (b) Hyaff11p80, wherein the admixture is injectable through the skin of a patient and the Hyaff11p80 is solubilized in organic solvent.
101. The composition of claim 98, further comprising TCP.	59. The composition of claim 57, further comprising TCP.

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New Claim	Original Claim/Support in Specification
<p>102. The composition of claim 98, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, and BMP-12.</p>	<p>60. The composition of claim 57, wherein the osteogenic protein is BMP-2. 61. The composition of claim 57, wherein the osteogenic protein is BMP-4. 62. The composition of claim 57, wherein the osteogenic protein is BMP-5. 63. The composition of claim 57, wherein the osteogenic protein is BMP-6. 64. The composition of claim 57, wherein the osteogenic protein is BMP-7. 65. The composition of claim 57, wherein the osteogenic protein is BMP-8. 66. The composition of claim 57, wherein the osteogenic protein is BMP-9. 67. The composition of claim 57, wherein the osteogenic protein is BMP-10. 68. The composition of claim 57, wherein the osteogenic protein is BMP-11. 69. The composition of claim 57, wherein the osteogenic protein is BMP-12.</p>
<p>103. A composition for delivery of osteogenic proteins to a patient comprising an osteogenic protein and Hyaff11p65, wherein the composition is injectable through the skin of the patient.</p>	<p>14. A composition for delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising (a) an osteogenic protein; and (b) an injectable hyaluronic acid ester, wherein the hyaluronic acid ester is Hyaff11p65, and wherein the admixture is injectable through the skin of the patient.</p>

Appendix A--Chart Showing Support for New Claims

New Claim	Original Claim/Support in Specification
<p>104. The composition of claim 103, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, BMP-10, BMP-11, and BMP-12.</p>	<p>28. The composition of claim 14, wherein the osteogenic protein is BMP-2.</p> <p>29. The composition of claim 14, wherein the osteogenic protein is BMP-4.</p> <p>30. The composition of claim 14, wherein the osteogenic protein is BMP-5.</p> <p>31. The composition of claim 14, wherein the osteogenic protein is BMP-6.</p> <p>32. The composition of claim 14, wherein the osteogenic protein is BMP-7.</p> <p>33. The composition of claim 14, wherein the osteogenic protein is BMP-8.</p> <p>34. The composition of claim 14, wherein the osteogenic protein is BMP-9.</p> <p>35. The composition of claim 14, wherein the osteogenic protein is BMP-10.</p> <p>36. The composition of claim 14, wherein the osteogenic protein is BMP-11.</p> <p>37. The composition of claim 14, wherein the osteogenic protein is BMP-12.</p>
<p>105. The composition of claim 103, wherein the Hyaff11p65 is solubilized in aqueous buffer.</p>	<p>77. (Previously presented) A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <p>(a) an osteogenic protein; and</p> <p>(b) Hyaff11p65,</p> <p>wherein the admixture is injectable through the skin of a patient and the Hyaff11p65 is solubilized in aqueous buffer.</p>
<p>106. The composition of claim 103, further comprising TCP.</p>	<p>78. (Previously presented) A composition for injectable delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <p>(a) an osteogenic protein;</p> <p>(b) Hyaff11p65; and</p> <p>(c) TCP,</p> <p>wherein the admixture is injectable through the skin of a patient.</p>
<p>107. A composition for delivery of osteogenic proteins to a patient comprising BMP-12 and Hyaff11p65, wherein the composition is injectable through the skin of the patient.</p>	<p>16. A composition for delivery of osteogenic proteins to a patient comprising a pharmaceutically acceptable admixture comprising</p> <p>(a) BMP-12; and</p> <p>(b) an injectable hyaluronic acid ester,</p> <p>wherein the hyaluronic acid ester is Hyaff11p65, and wherein the admixture is injectable through the skin</p>

Appendix A--Chart Showing Support for New Claims

New Claim	Original Claim/Support in Specification
	of the patient.